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NEPHROLOGY FORUM

The kidney and magnesium regulation

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Case presentations

Patient 1. A 33-year-old woman was admitted to St. Paul's Hospital in Vancouver, B.C. with cramps in her hands and feet. An intestinal bypass operation had been performed 4 years earlier because of obesity (her weight was 122.5 kg prior to operation). A cholecystectomy had been performed at the same time. Over the next 2 years she lost 61.2 kg and was well except for episodic diarrhea. One year prior to the present admission, she had been admitted to the hospital; the serum magnesium was 0.56 mEq/liter and calcium was 6.6 mg/dl. Serum magnesium was corrected over 24 hours with magnesium sulfate to 2.16 mEq/liter, and the serum calcium level rose spontaneously to 8.2 mg/dl over 3 days.

A few weeks prior to the present admission, her bowel movements increased to 20 to 30 per day, and she noticed progressive weakness, cramps in her hands, and circumoral numbness. On admission, blood pressure was 130/90 mm Hg; pulse rate was 80 lying and standing. The only abnormal physical finding was a positive Chvostek's sign. Laboratory results were as follows: sodium, 144 mEq/liter; potassium, 3.1 mEq/liter; chloride, 109 mEq/liter; total CO_2, 29 mmol/liter; BUN, 7 mg/dl; serum creatinine, 0.7 mg/dl; calcium, 6 mg/dl (normal, 8.6–10.3); magnesium, 0.4 mEq/liter (normal, 1.4–2.10); total protein, 5.6 g/dl; and serum albumin, 3.3 g/dl. Hemoglobin was 11 g/dl. Serum vitamin B_{12}, serum folate, and serum parathyroid hormone were normal. Results of urinalysis were normal. A spot urine magnesium concentration was 0.5 mEq/liter. Electrocardiogram was normal, including the QT interval.

Because of marked hypomagnesemia, hypocalcemia, and tetany, the patient was given 8 mEq of magnesium as 50% magnesium sulfate hourly for 6 hours and then 8 mEq every 4 hours; she also received 25 mEq of potassium chloride twice daily. Serum magnesium rose to 0.96 mEq/liter within 3 hours and to 3.6 mEq/liter after 11 hours. She was given 500 mg of calcium salts three times daily, and the plasma calcium rose to 8.6 mg/dl. Potassium rose to 3.5 mEq/liter. All signs and symptoms of hypomagnesemia and hypocalcemia disappeared and remained absent while she received 48 mEq of magnesium per day. The 24-hour urinary magnesium excretion rose to 42 to 50 mEq/liter; this value reflects a fractional urinary magnesium excretion of 28% to 42%.

Patient 2. A 36-year-old woman was hospitalized at Vancouver General Hospital because of lower abdominal distension. The only previous medical problem was hyperthyroidism. She had been treated with ^{131}I one year prior to admission and was maintained on replacement therapy with l-thyroxine. On admission, pelvic examination disclosed bilateral ovarian masses; a subsequent laparotomy revealed bilateral ovarian papillary cystadenomas with small omental and hepatic metastases. Hysterectomy and bilateral salpingo-oophorectomy were performed. She was treated with seven cycles of melphalan over 8 months; a second laparotomy disclosed no remaining tumor. Subsequently she was given eight cycles of doxorubicin and cisplatin, a total of 625 mg of each drug, for 7 months. A third laparotomy disclosed a 1 cm lesion on the anterior wall of the sigmoid colon and a 0.4 cm nodule in the right paracolic gutter. The tumor was a poorly differentiated adenocarcinoma, presumably a metastasis from the original lesion. The patient was given a course of radiotherapy.

She was readmitted to the hospital 20 months later with a 2-week history of malaise, fatigue, bruising, dyspnea on exertion, and hematochezia. Hemoglobin was 6 g/dl; platelet count was 15,000/mm^3; and she had 20% blast cells on peripheral smear. Bone-marrow biopsy showed acute nonlymphocytic leukemia with 82% blast cells. Chromosomal analysis revealed a pattern not previously reported in humans. She was diagnosed as having chemotherapy-induced leukemia, and drug therapy was begun; she also received a bone-marrow transplant from an identical twin with complete HLA, red cell genotype, and mixed-lymphocyte culture compatibility.

A low serum magnesium concentration (1.2 mEq/liter; normal range, 1.8–2.8 mEq/liter) was documented for the first time just prior to bone-marrow transplantation. Serum calcium was 9.6 mg/dl; phosphate, 4.1 mg/dl; total protein, 6.3; and albumin, 2.7 g/dl. Preparation for bone-marrow transplantation included treatment with methotrexate, cyclophosphamide with concurrent furosemide diuresis, and bladder irrigation. She also received tobramycin, carbenicillin, and radiotherapy. Serum magnesium fell to 0.6 mg/dl, and she required continuous magnesium supplementation over the next several weeks. Following bone-marrow transplantation, she developed pseudomonas septicemia, which was treated with amikacin, piperacillin, and cefazolin. She also developed candida septicemia requiring treatment with 1.2 g of amphotericin B. Hypomagnesemia persisted and hypokalemia developed. Hemolytic anemia became apparent, and bone-marrow aspiration revealed hypocellular marrow. At discharge, the patient was given prednisone, potassium supplements, and 15 ml of magnesium glucoheptonate thrice daily (225 mg of elemental magnesium per day).

Two months later, weakness, fatigue, dizziness on standing, and dyspnea on exertion prompted her readmission to the hospital. She had decreased appetite and increased thirst. Physical examination revealed a pale 40-year-old woman with marked oral candidiasis, but otherwise physical examination was normal. The hemoglobin was 4.6 g/dl. Serum

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hemoglobin was 53 mg/dl; haptoglobin, 10 mg/dl; serum sodium, 136 mEq/liter; potassium, 2.9 mEq/liter; chloride, 105 mEq/liter; bicarbonate, 23 mEq/liter; magnesium, 0.4 mg/dl; and albumin, 3.4 g/dl. Prednisone was increased to 100 mg daily and the patient was transfused with 4 units of packed cells. The administration of 10 g of magnesium sulfate intravenously over the next 16 hours resulted in an increase in serum magnesium to 1.2 mg/dl. Hemoglobin stabilized at 10 g/dl. The dietary magnesium intake of 250 to 300 mg/day was supplemented with 75 ml of magnesium glucoheptonate (375 mg of elemental magnesium per day). Prior to the patient's discharge, the serum calcium was 8.8 mg/dl; magnesium, 0.8 mg/dl; phosphate, 3.7 mg/dl; serum creatinine, 0.8 mg/dl; potassium, 4.0 mEq/liter; and hemoglobin, 10 g/dl. Twenty-four hour urinary magnesium excretion was approximately 120 mg; of calcium, 185 mg; and of potassium, 60 mEq. The creatinine clearance was 65 ml/min and the fractional magnesium excretion was 29.2%; fractional calcium and potassium excretions were 0.5% and 27.6%, respectively. Two weeks later, serum magnesium, potassium, calcium, and hemoglobin levels were stable.

Discussion

DR. JOHN H. DIRKS *(Professor and Head, Department of Medicine, University of British Columbia and Vancouver General Hospital, Vancouver, B.C., Canada):* These 2 patients presented with complicated histories but both had profound, symptomatic hypomagnesemia requiring treatment with magnesium salts. Two different mechanisms for hypomagnesemia are illustrated. The first patient's low serum magnesium was due to gastrointestinal malabsorption and marked diarrhea. The greatly reduced serum magnesium and serum calcium levels resulted in all the clinical hallmarks of neuromuscular irritability such as carpopedal spasm and Chvostek's sign. The kidney in this patient responded appropriately to hypomagnesemia and conserved magnesium maximally. In contrast, the hypomagnesemia in the second patient was due to a persistent renal magnesium leak; she had concomitant hypocalcemia and hypokalemia. These two patients provide the backdrop for our discussion of the role of the kidney in normal magnesium homeostasis and the relationship of magnesium to calcium and potassium metabolism. I will return to these two patients after discussing normal and abnormal renal magnesium handling.

Normal renal handling of magnesium

Magnesium has been the forgotten cation. It is the fourth most abundant cation in the body and the second most abundant (after potassium) in the cells. Total-body magnesium is approximately 24 g; bone and skeletal muscle are the major reservoirs for magnesium, containing 60% and 20% respectively, but most cellular magnesium is not readily exchangeable. Serum magnesium is carefully regulated between 1.4 and 2.1 mEq/liter (0.7–1.0 mM or 1.7–2.3 mg/dl). Normally we ingest approximately 300 mg (25 mEq) of magnesium per day, and about one-third of the intake is absorbed by the gastrointestinal tract. Renal magnesium handling is essentially a filtration-reabsorption process even though magnesium secretion has been suggested [1, 2]. The data supporting magnesium secretion still are not compelling, and if magnesium secretion occurs it contributes only in a minor way to overall magnesium balance. Eighty percent of the serum magnesium is ultrafilterable (of which 70% to 80% is ionized). Over a 24-hour period, 3500 mg of magnesium is filtered; in humans only about 3% of this amount is excreted in the urine, or approximately 100 to 150 mg/day (8–15 mEq/day), an amount equal to that absorbed by the gastrointestinal tract each day.

Micropuncture studies have disclosed considerable information about magnesium reabsorption in the various nephron segments [3]. In the proximal tubule, the magnesium concentration rises along the length of the tubule and attains a value 1.5 times that in an ultrafiltrate of plasma [4]. This is unlike sodium or calcium: sodium concentration in the proximal tubule is essentially identical to an ultrafiltrate of plasma; the calcium concentration rises only 10% to 20% above that in the ultrafiltrate. The high tubular fluid/ultrafiltrate (TF/UF) magnesium in the proximal tubule remains unaltered despite changes in plasma magnesium and calcium. The high concentration of magnesium in the proximal tubule fluid reflects the very low permeability of the proximal tubule epithelium to magnesium. Magnesium reabsorption in the proximal tubule is largely a unidirectional process, and the rate of reabsorption is directly related to the concentration of magnesium in the luminal fluid. The proximal tubular reabsorption of magnesium is only 25% to 30% of the filtered load, in contrast to 50% to 60% of the filtered load for sodium and water (accounting for the TF/UF magnesium of 1.5). However, overall absolute reabsorption of magnesium is proportional to proximal sodium and water reabsorption. Details of the cellular process of reabsorption of magnesium in the proximal tubule remain largely unknown.

Magnesium concentration continues to rise as the tubular fluid traverses the descending limb of Henle's loop and can reach a concentration three- to fourfold that of the plasma ultrafiltrate [5, 6]. Thus, relatively higher concentrations of magnesium (compared to plasma ultrafiltrate) enter the ascending limb than of other ions.

The thick ascending limb of Henle's loop is now known to be the major site of magnesium reabsorption in the renal tubule and the principal locus of renal control of magnesium excretion. LeGrimellec, Roinel, and Morel observed in 1973 that magnesium concentration in the early distal tubule fluid was well below the plasma ultrafiltrate [4]. Distal tubular fluid to ultrafiltrate magnesium concentration ratios were calculated at approximately 0.6. Coupled with the marked water reabsorption that takes place before this site in the nephron, a TF/UF magnesium ratio of 0.6 indicates that 50% to 60% of the filtered magnesium is reabsorbed between the thin descending limb and the early distal tubule, a fractional reabsorption much greater than that of sodium or calcium. The thick ascending limb of Henle's loop appears to be the segment responsible for the bulk of the observed magnesium reabsorption.

Recent in-vitro microperfusion studies confirm that net magnesium reabsorption does take place in the thick ascending limb of Henle's loop and is voltage dependent [7]. Such microperfusion studies have given us considerable knowledge of the characteristics of the reabsorption of magnesium in the thick ascending limb of the loop of Henle [8]. We observed that when the luminal concentration of magnesium was elevated progressively, the loop of Henle reabsorbed progressively more magnesium, maintaining a fractional reabsorption rate of 80% of the delivered load. However, when plasma magnesium was elevated with intravenous infusions of magnesium salts, the ability of the loop of Henle to reabsorb progressively more magnesium was sharply blunted, presumably because magnesium reabsorption was retarded at the basolateral border of the thick ascend-

ing limb cells by the elevated peritubular capillary magnesium levels. Also, as plasma magnesium was raised, calcium reabsorption by the loop of Henle was progressively reduced; sodium reabsorption remained at relatively normal levels until magnesium concentration was elevated to more than 10 mEq/liter. The loop of Henle thus has a marked intrinsic ability to reabsorb progressively more concentrated solutions of magnesium. Its reabsorptive capacity decreases, however, as plasma magnesium rises, allowing more and more magnesium to escape into the urine. In fact, most of the additional magnesium delivered to the early distal tubule is excreted in the urine.

The microperfusion experiments I just described were compared with similar free-flow micropuncture experiments performed earlier in the dog. Massry, Coburn, and Kleeman have described a maximal renal reabsorption rate (Tm) for magnesium as plasma magnesium is progressively elevated [9]. The micropuncture experiments suggest that this apparent Tm was a fortuitous occurrence. When the plasma magnesium level rose, proximal reabsorption of magnesium continued to increase, but magnesium reabsorption in the loop of Henle rose initially but fell to zero at the highest plasma magnesium levels. The sum of rising magnesium reabsorption in the proximal tubule and falling magnesium reabsorption in the loop of Henle yielded a leveling off of magnesium reabsorption with increasing plasma magnesium, that is, an apparent Tm. Although fortuitous, this apparent Tm relationship is useful in assessing overall renal magnesium handling.

Micropuncture studies of the distal convoluted tubule indicate a limited reabsorptive capacity for magnesium [4, 6, 8]. As the load of magnesium delivered to the distal tubule is increased, the amount of magnesium reabsorbed initially increases but, because of saturation of the reabsorptive system, any further increase in load is excreted in the urine. The total magnesium reabsorbed in the distal convoluted tubule is less than 5% of that filtered. Studies of magnesium reabsorption in the cortical collecting tubules and collecting ducts indicate that little magnesium is reabsorbed at these sites. There may be some nephron heterogeneity, however, and deep nephrons might contribute more to urinary magnesium excretion.

In conclusion, the principal sites of normal tubular magnesium reabsorption in the nephron are the proximal tubule and the loop of Henle, with the major site being the thick ascending limb. Major factors affecting renal magnesium excretion are summarized in Table 1.

Table 1. Major factors controlling magnesium excretion

GFR and filtered load
Extracellular fluid volume
Hypermagnesemia
Hypomagnesemia
Phosphate depletion
Hypercalcemia
Parathyroid hormone

The renal response to hypomagnesemia and magnesium deficiency

Although hypomagnesemia does not necessarily reflect cellular magnesium depletion, it usually indicates a certain amount of magnesium deficiency [10]. When hypomagnesemia occurs, the filtered load of magnesium progressively declines with the fall in serum magnesium concentration. Using micropuncture techniques, we studied severe magnesium depletion in a rat model and found that the magnesium concentration in the proximal tubule rose in an identical fashion to that occurring under normal circumstances [11]. Because the luminal magnesium concentration is diminished, however, absolute reabsorption of magnesium is greatly reduced even though the fractional magnesium reabsorption remains at 25% to 30% in the proximal tubule. Our studies of the loop of Henle in magnesium-depleted rats indicate that magnesium reabsorption was more complete in the loop of Henle than under normal circumstances. Magnesium concentrations in the early distal tubule fluid were extremely low (approximately TF/UF Mg 0.4) and overall reabsorption at this point in the nephron was over 95% of that filtered. Thus the loop of Henle was the site in the nephron where the major additional conservation of magnesium took place. In this rat model of magnesium depletion, in which 30% of body magnesium was lost and serum magnesium was diminished by 50%, fractional excretion of magnesium was reduced from a normal in the rat of about 15% to approximately 3%. When the plasma magnesium was rapidly elevated with intravenous magnesium infusions, plasma magnesium rose promptly and the kidney rapidly excreted large amounts of the infused magnesium. The data suggested, in fact, that there was some delay in the ability of the loop of Henle to reabsorb magnesium as avidly as one might expect, and this finding might reflect a mild cellular defect because of the magnesium depletion.

The renal response to hypermagnesemia

I already have alluded to some of the kidney's responses to hypermagnesemia. In induced hypermagnesemia, fractional magnesium reabsorption is reduced modestly in the proximal tubule because of the modest inhibitory effect of elevated plasma magnesium on net sodium and water reabsorption. The major decrease in magnesium reabsorption takes place in the loop of Henle, however. In fact, if plasma magnesium is raised enough, magnesium reabsorption in the loop of Henle can approach zero, as I noted earlier. Our experimental data indicate that the effect of elevated plasma magnesium is on the basolateral side of the cell; raising magnesium concentration on the luminal side alone does not reduce magnesium reabsorption. The greatly increased load of magnesium delivered to the distal nephron exceeds the transport capability of the distal nephron segments, and most of the magnesium rejected in the loop of Henle is excreted into the urine. Some data suggest that magnesium may be added to the descending limb of the deep nephrons in hypermagnesemia and perhaps to the collecting duct system, but on balance the data are inconclusive. There is no question that the major site of reduced magnesium reabsorption in hypermagnesemia is the thick ascending limb of Henle's loop.

Interrelationship of magnesium and calcium reabsorption

Hypercalcemia causes not only hypercalciuria but also hypermagnesiuria. As I mentioned, hypermagnesemia also leads to marked hypercalciuria as well as hypermagnesiuria. Our microperfusion data in the rat point to the loop of Henle as the site where the competition of calcium and magnesium for

transport occurs. The cellular site probably is the basolateral membrane even though this interaction was not confirmed in in-vitro microperfusion studies in the rabbit [7]. We hypothesize that there is a competitive active transport process sensitive to the absolute concentration of calcium and magnesium in the interstitial fluid and that this process is somewhat more sensitive to magnesium than to calcium. The transport system has a more important effect on magnesium excretion than it does on calcium excretion. This hypothesis makes it important that one keep in mind the effects of both plasma calcium and magnesium concentrations whenever a maneuver is utilized that alters the excretion of these cations. One must be sure that the derangements of calcium and magnesium excretion are not due to altered plasma calcium or magnesium levels.

The effects of hypomagnesemia and hypocalcemia on magnesium and calcium reabsorption in the loop of Henle have not been studied to as great an extent as have the effects of hypermagnesemia and hypercalcemia. Hypocalcemia may augment calcium and magnesium reabsorption, however [2, 3]. Thus, the competitive transport system for calcium and magnesium in the loop of Henle allows greater levels of calcium and magnesium reabsorption when either the plasma calcium or magnesium concentration is depressed. Patients with familial hypocalciuric hypercalcemia also have hypermagnesemia [12], and it is tempting to speculate that the calcium-magnesium transport system might be less sensitive to the inhibitory action of elevated plasma calcium and magnesium concentrations in these interesting patients.

The effect of extracellular fluid volume on magnesium excretion

The proximal tubule is sensitive to changes in extracellular fluid volume, largely because of alterations in transcapillary forces that affect the degree of sodium backflux, and hence net sodium and water reabsorption. Magnesium reabsorption is similarly affected by changes in extracellular volume, presumably via changes in the intraluminal magnesium concentration in turn determined by net sodium and water reabsorption. We observed in microperfusion experiments that, as flow rate to the loop of Henle is progressively increased, fractional magnesium reabsorption is reduced at this site [3]. I believe that an increase in flow rate to the loop of Henle reduces the transtubular sodium gradient and electrical potential, which may account for the lower fractional reabsorption, as magnesium reabsorption is largely voltage dependent. Overall, volume expansion causes a much greater fractional increase in urinary magnesium excretion than in urinary sodium excretion.

Diuretics and magnesium excretion

Carbonic anhydrase inhibitors blunt magnesium reabsorption in the proximal tubule, but the extra magnesium delivered to the loop of Henle is largely recaptured there so that virtually no increase in urinary magnesium excretion occurs [13]. Thiazide diuretics initially can cause a small increase in magnesium excretion, but this usually is not sustained [14]. The most potent diuretic agents that affect magnesium excretion are the osmotic diuretics such as mannitol and urea [15, 16] and the loop diuretics such as furosemide and ethacrynic acid [17]. The osmotic diuretics principally reduce magnesium reabsorption in the loop, an effect probably related to the greatly diminished sodium chloride and water reabsorption. Loop diuretics, such as furosemide, markedly inhibit magnesium reabsorption, again probably secondary to diminished sodium chloride and water reabsorption. When fractional reabsorption rates are compared, magnesium reabsorption is reduced relatively more than that of calcium and calcium reabsorption more than that of sodium.

Parathyroid hormone and magnesium excretion

Parathyroid hormone is the principal hormone that affects renal magnesium reabsorption. The latest studies suggest that parathyroid hormone enhances tubular magnesium reabsorption and that the effect takes place in the loop of Henle and the distal convoluted tubule; this has been most clearly shown in the golden hamster, which is very sensitive to the action of parathyroid hormone [18]. Following parathyroidectomy in this species, calcium and magnesium excretion rose to 20% of the filtered load, a change rapidly reversed by the administration of parathyroid hormone or cyclic AMP. The effects of parathyroid hormone on magnesium transport, however, are readily overcome by more important factors such as hypercalcemia and hypermagnesemia. Whether parathyroid hormone plays a role in the normal day-to-day regulation of renal magnesium reabsorption is unclear.

Other factors that may influence magnesium excretion

Renal potassium wasting is a well-established accompaniment of hypomagnesemia and magnesium depletion. Whether this association is due to secondary hyperaldosteronism or to direct influences on cellular potassium metabolism is not known, but derangements in potassium balance are commonly noted with altered magnesium homeostasis [19].

A number of other circumstances also affect magnesium excretion. Phosphate depletion can result in significant magnesiuria [1, 3]. Acute acidosis may increase magnesium excretion, which can be corrected by alkali infusions [20]. A number of hormonal agents such as thyroid hormone, calcitonin, and vitamin D metabolites can have extrarenal influences on magnesium metabolism [1, 3]. Alcohol can increase magnesium excretion in some instances [21]. Urinary magnesium wasting is a frequently observed consequence of the chronic use of drugs such as cisplatin, gentamicin, and perhaps amphotericin [22, 23].

Summary of renal handling of magnesium

Renal magnesium transport is altered by changes in plasma magnesium and plasma calcium and by changes in extracellular fluid volume. Loop diuretics and osmotic diuretics can profoundly reduce magnesium reabsorption. Evidence supports the contention that parathyroid hormone can enhance magnesium reabsorption in the nephron. Interrelationships of hypomagnesemia and magnesium depletion to overall calcium and potassium metabolism are complex but appear to be dependent on tissue magnesium concentration.

Clinical causes of hypomagnesemia

I now would like to return to today's 2 patients with hypomagnesemia. They represent the two broad clinical mechanisms of hypomagnesemia: defective gastrointestinal absorption of magnesium and renal magnesium wasting. The first patient,

Table 2. Gastrointestinal causes of hypomagnesemia

Malabsorption syndromes
Protein calorie malnutrition
Alcoholism
Prolonged gastrointestinal suction
Prolonged intravenous therapy

Table 3. Renal magnesium wasting

Primary renal magnesium wasting
Loop diuretics
Diabetic ketoacidosis (osmotic diuresis)
Bartter's syndrome
Hyperaldosteronism
Syndrome of inappropriate ADH secretion
Alcoholism
Hypercalciuria or salt-wasting states
Amphotericin toxicity
Aminoglycosides (gentamicin)
Cisplatin

who had a small-bowel bypass for obesity, illustrates one cause of defective intestinal absorption of magnesium (Table 2). Other gastrointestinal causes include idiopathic steatorrhea, various diseases of the distal ileum with or without resection, biliary fistula, and partial gastric resection. Poor gastrointestinal absorption also can occur as an isolated hereditary defect [24] or in association with malnutrition, especially protein deficiency. Alcoholics develop hypomagnesemia because of poor dietary magnesium intake, but also because of increased renal magnesium excretion. Hypomagnesemia also can occur during prolonged intravenous therapy with fluids containing insufficient magnesium.

The first patient had hypomagnesemia severe enough to cause all the common physical signs of neuromuscular irritability associated with hypomagnesemia and hypocalcemia. She had associated mild hypokalemia. Treatment with magnesium sulfate rapidly corrected the low serum magnesium, and her serum calcium level rose spontaneously without administration of additional calcium. The latter effect may be the result of increased secretion of parathyroid hormone or increased cellular sensitivity to parathyroid hormone following magnesium repletion [25]. We should note that the measured parathyroid hormone levels were still in the normal range in the presence of the severe hypocalcemia, suggesting impairment of PTH secretion. Initially the urine magnesium was exceedingly low, reflecting intense renal conservation of magnesium. The fractional excretion of magnesium rose sharply when supplemental magnesium was given, however, indicating inefficient renal retention of needed magnesium.

The second patient with hypomagnesemia represents an instance of renal magnesium wasting. As indicated in Table 3, there are many causes of renal magnesium wasting. These include a primary defect in renal magnesium reabsorption (which may be an inherited disorder [26]), magnesium wasting associated with the osmotic diuresis of diabetic ketoacidosis, and a variety of other clinical disorders such as Bartter's syndrome. Magnesium wasting frequently accompanies vigorous diuresis such as that occurring in hypercalcemic patients given furosemide. It also can accompany the use of certain antimicrobial and chemotherapeutic agents such as gentamicin [23], amphotericin B [22], and cisplatin [27]. Our second patient is, indeed, very complicated, because the ovarian cancer was treated with a variety of chemotherapeutic agents, including cisplatin. She then developed a nonlymphocytic leukemia and, because of the associated candida infections, required amphotericin B therapy. The inappropriately high values for urinary magnesium during hypomagnesemia in this patient indicated that she had a renal magnesium-wasting disorder. The magnesium wasting probably resulted from the effects of cisplatin and was aggravated by the concomitant diuretic and antimicrobial drug therapy.

Several groups have reported magnesium wasting in patients receiving cisplatin. Schilsky and Anderson in 1979 found hypomagnesemia in 23 of 44 patients receiving cisplatin [27]. Cisplatin can cause other types of renal damage such as acute tubular necrosis. Amphotericin B is thought to cause mild hypomagnesemia. There is no question that the patient had chronic tubular damage in the segments responsible for magnesium reabsorption, as she continued to have low serum magnesium levels because of a renal magnesium leak. The site of this defective magnesium reabsorption is completely conjectural at this time, but one could postulate that the defect resides in the thick ascending limb, where the principal amount of magnesium reabsorption normally takes place. However, if the proximal tubular damage were severe enough and if the delivery of filtrate to the loop of Henle were sufficiently high, then the magnesium absorptive capacity of the loop of Henle could be overwhelmed. This patient also had hypokalemia and hypocalcemia, which are not readily explained. The interrelationship of magnesium and calcium is similar to that in the first patient; that is, there may be both resistance to the action of parathyroid hormone and impairment of parathyroid hormone secretion [25]. The magnitude of the potassium losses seems too great to ascribe to the effects of hypomagnesemia alone and might reflect additional toxicity due to amphotericin B as well as cisplatin. Whether other aspects of the patient's condition, such as her repetitive attacks of hemolysis, are related to hypomagnesemia remains unanswered.

Questions and answers

DR. DAVID PARKINSON *(Hematology/Oncology Division, NEMC):* Dr. Dirks, other heavy metals such as selenium and gallium are now in the first phase of testing as potential antineoplastic agents. Would you expect that such heavy metals, which are known to be nephrotoxic, also might affect magnesium transport?

DR. DIRKS: I know of no data indicating that any of these agents affect magnesium transport in experimental animals or in humans in the same manner as cisplatin, although certainly such data would be important.

DR. ROBERT SCHWARTZ *(Chief, Hematology/Oncology Division, NEMC):* Is it likely that the administration of aminoglycosides contributed to the renal problems in the second patient presented?

DR. DIRKS: I believe that the major cause of the magnesium wasting was cisplatin administration, although other factors such as aminoglycosides also might have played a role. There

are reports of hypomagnesemia occurring with gentamicin alone [23].

DR. SCHWARTZ: Dr. Parkinson, do you think it appropriate to use tobramycin in patients who are receiving cisplatin?

DR. PARKINSON: No, I don't think that aminoglycosides and cisplatin should be used together. Cisplatin and gentamicin in combination can result in severe nephrotoxicity [28]. Because cisplatin can persist in the kidney for as long as one year, it might even be prudent to avoid the use of aminoglycosides in patients who received cisplatin in the recent past if possible. I am not aware, however, of specific information concerning the interaction of tobramycin with cisplatin.

DR. JEROME P. KASSIRER: Do we know the precise cause of magnesium wasting in patients given aminoglycosides? Where is the specific tubular defect of magnesium reabsorption?

DR. DIRKS: Available studies do not provide an exact answer to this question. We do know, however, that the renal toxicity of aminoglycosides is directed primarily at the proximal tubule. One might imagine that reduced magnesium reabsorption in the proximal tubule would increase magnesium delivery to the loop of Henle, and that this increase would exceed the reabsorptive capacity of the loop, thereby resulting in magnesiuria. Alternatively, defective reabsorption could occur within the loop of Henle.

DR. KASSIRER: Would you comment on the mechanisms of potassium wasting in magnesium deficiency?

DR. DIRKS: Hypokalemia and potassium depletion are commonly thought to accompany magnesium deficiency. The initial studies of Welt, in which hypomagnesemia and magnesium depletion were produced in rats by dietary magnesium deprivation, showed that potassium depletion was a frequent accompaniment [29]. The mechanism responsible for the hypokalemia and potassium depletion is not understood and frequently has been attributed to defective potassium handling by the kidney. In our own studies in magnesium-depleted rats, we did not find renal potassium wasting. Micropuncture studies of the distal tubule confirmed that potassium transport was essentially normal. Thus, the potassium depletion that occurs with magnesium deficiency is not due to altered renal potassium handling but might reflect defective magnesium-potassium transport at the cellular level.

DR. JOHN T. HARRINGTON: Is it possible that the "self-depression" of magnesium absorption by the nephron in hypermagnesemic experimental animals is due to elevated magnesium levels in the peritubular capillaries? Could such high concentrations have a direct effect on magnesium transport across the thick ascending limb?

DR. DIRKS: Our studies suggest that hypermagnesemia in the peritubular capillaries, and therefore in the interstitial fluid, is indeed responsible for the "self-depression" of magnesium transport. In our in-vitro microperfusion studies of the loop and our free-flow studies of proximal and early distal tubule magnesium reabsorption, progressive elevations in plasma magnesium caused a progressive decline in magnesium reabsorption within the loop of Henle. We postulate that a high magnesium level can inhibit magnesium reabsorption across the contraluminal aspect of the tubular cell. The recent in-vitro microperfusion experiments of Shareghi and Agus confirm this finding: raising the magnesium concentration in the fluid in which the tubule was immersed reduced magnesium reabsorption [7]. Elevating magnesium concentration in the lumen has the opposite effect: it increases reabsorption.

DR. HARRINGTON: What is the evidence for magnesium secretion in the nephron?

DR. DIRKS: Micropuncture studies performed by LeGrimellec and colleagues [30] as well as by us revealed instances in which more magnesium appeared in the urine than was present in the late distal tubule [31]. This finding suggested that there was magnesium secretion somewhere in the collecting ducts. These observations also could be explained, of course, by nephron heterogeneity. Further, puncture of the cortical collecting tubules by Brunette and colleagues did not demonstrate magnesium secretion [32]. Our own recent micropuncture studies detected little evidence of magnesium backflux into the lumen. The general conclusion has been that magnesium secretion, if it occurs, is of minor importance in the physiologic regulation of magnesium excretion. It is better to think of the nephron as able to reduce its magnesium reabsorption almost to zero when required. However, if the clearance studies reported in the literature are taken at face value, the possibility of magnesium secretion remains. It will be important to test individual nephron segments by in-vitro perfusion experiments in the presence of a high bath magnesium concentration to demonstrate more unequivocally whether magnesium secretion occurs.

DR. DAVID CAHAN *(Chief, Nephrology Division, Faulkner Hospital, Boston):* Dr. Dirks, are there any important interrelationships between magnesium and phosphate metabolism?

DR. DIRKS: Magnesiuria can occur during phosphate depletion. Coburn and Massry observed this phenomenon in their studies of phosphate depletion in the dog [33]. In our micropuncture studies in the dog, magnesium excretion appeared normal during phosphate depletion but decreased significantly when phosphate stores were repleted and when parathyroid hormone levels were restored to normal [34].

DR. NICOLAOS E. MADIAS: Could you comment on the changes in renal magnesium handling in patients who are being treated chronically with thiazides?

DR. DIRKS: Magnesium excretion tends to remain normal or increase slightly immediately after thiazide administration [17]. Mild magnesiuria can occur in patients being treated chronically with thiazides [35]. In our micropuncture experiments in the hamster, thiazides caused no immediate change in magnesium reabsorption even though the expected natriuretic and calcium-retaining effects of the agent in the distal tubule could be demonstrated [14]. The reason for the persistent magnesiuria in some patients who chronically receive thiazides is not clear, but it might be related to an effect of thiazides on distal magnesium transport too small to be detected during acute experiments, or to increased delivery to distal sites of magnesium escaping loop reabsorption.

DR. HARRINGTON: Dr. Dirks, magnesium-depleted rats become hypercalcemic, not hypocalcemic as do magnesium-depleted humans. Could you comment on the reasons for this species difference?

DR. DIRKS: As I discussed, the hypocalcemia that occurs in hypomagnesemia in humans is a complex affair involving defective PTH secretion, insensitivity of the bone to PTH, and defective exchange between the extracellular fluid and the

bone. These mechanisms have not been studied in detail in the rat and might not be as impaired.

DR. MADIAS: Could you please comment further on the effect of hypomagnesemia on PTH secretion. Some experimental evidence suggests that this effect might be influenced by the degree of decline in magnesium concentration.

DR. DIRKS: This appears to be true, as initially hypomagnesemia increases PTH secretion, but more profound hypomagnesemia reduces PTH secretion. Correction of plasma magnesium is often necessary to correct blunted PTH secretion and hypocalcemia, as in the first patient presented [36].

DR. CAHAN: What happens when patients with familial hypocalciuric hypercalcemia are given magnesium?

DR. DIRKS: There are not enough observations of this type to answer your question with certainty. It would appear that magnesium infusion in such patients results in more magnesium retention at any plasma level of magnesium. Of course, when plasma magnesium concentration is raised sufficiently, magnesiuria occurs.

DR. MADIAS: Does hypermagnesemia or hypomagnesemia exert any important influence on PTH secretion and the level of serum calcium in patients with chronic renal insufficiency?

DR. DIRKS: Hypermagnesemia probably does not exert an important effect on PTH secretion in patients with renal insufficiency; however, hypocalcemia secondary to hypomagnesemia has been observed in patients with renal failure as well as in patients with normal renal function.

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